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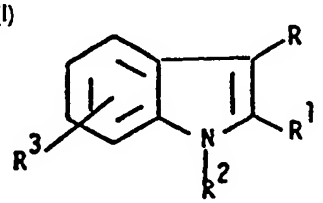
(54) Indole derivatives, their preparation and use as medicaments

(57) Compounds of formula (I)

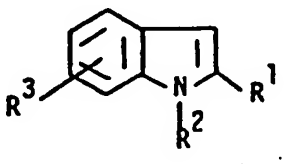


(I)

in which R and R^1 represent:

$$(CH_2)_m\text{–}X\text{–}CHR^4(CH_2)_nR^5$$

with m and n respectively being 0 to 8; and m + n = 2 to 10; X=CH^2, CH=CH, R^4=H, OH; R^5=Me, CH_2OH, CHO, tetrazole, CH_2NH_2, $COOR^6$; R^6=H, Me, Et, benzyl, pivalyl, or other pharmaceutically acceptable ester forming groups; R^2 is H; a (C_1–C_6) alkyl; benzyl, 2–picolyl, 3–picolyl, 4–picolyl groups; $(CH_2)pR^7$ where p is 1 to 6, R^7=COOH, NHR^8, OH, SR^8 and R^8 being a (C_1–C_6) alkyl;
R^3 is H, halogen, (C_1–C_6) alkoxy; and salts thereof have been found to inhibit platelet aggregation of blood and can be formulated as compositions having anti-platelet aggregation and antithrombotic activities. Precursors of the above have the formula:-



(III)

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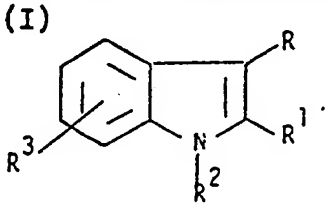
INDOLE DERIVATIVES, THEIR PREPARATION AND USE AS MEDICAMENTS

ADP, collagen, thrombin and arachidonic acid are known to favour platelet aggregation phenomena, causing formation of thrombi, which are the main cause of ischemic, cardiac and cerebral vasculopathies, peripheral arteriopathies on arteriosclerotic base, and/or venous thrombosis.

Therefore, substances which antagonize the effects thereof are most desirable for therapeutic use, for example in the preparation of compositions useful in medicine, particularly treatment of thrombopathies.

The present invention includes within its scope indole derivatives capable of inhibiting platelet aggregation phenomena, of general formula (I)



(I)

wherein R and R^1, which can be the same or different, are: $(CH_2)_m$-X-$CHR^4(CH_2)_nR^5$, in which m and n are an integer 0 to 8 and m + n are an integer 2 to 10; X=CH_2, CH=CH; R^4=H,OH; R^5=Me, CH_2OH, CHO, tetrazol, CH_2NH_2, $COOR^6$; R^6=H,Me,Et, benzyl, pivalyl groups or other groups forming a pharmacologically acceptable ester;

R^2 is H; a straight or branched chain (C_1-C_6) alkyl; benzyl, 2-picolyl, 3-picolyl, 4-picolyl groups; $(CH_2)_pR^7$ with p comprised from 1 to 6, in which R^7=COOH, NHR^8, OH, SR^8 and R^8 in its turn is a straight or branched chain (C_1-C_6) alkyl;

R^3 is H, halogen, straight or branched (C_1-C_6) alkoxy;

and all the possible optical and/or geometric isomers thereof.

The compounds of the invention are a novel class of indole derivatives characterized by the presence of alkyl or alkenyl chains consisting of at least 4 carbon atoms at the 2- and 3- positions. Preferably one of the two chains is characterized by the presence of a carboxy group $COOR^6$, wherein R^6 has the above mentioned meanings.

The invention also relates to pharmacologically acceptable salts of the compounds of formula (I) with cations, when R^6=H and/or R^7=COOH and with anions when R^5=CH_2NH_2 and/or R^7=NHR^8.

"Cation pharmacologically acceptable" salts can be prepared by techniques known to those skilled in the art, by means of organic or, better, inorganic bases. Inorganic base addition salts comprise salts formed with alkali and alkali earth metals such as calcium, magnesium, sodium, potassium, lithium or alluminium, ammonium and zinc salts; salts deriving from organic bases comprise salts formed with primary, secondary and tertiary amines, which can be substituted or cyclic amines, basic resins or amino acids, e.g. isopropylamine, trimethylamine, diethanolamine, diethylamine, triethylamine, ethanolamine, 2-diethylamino-ethanol, lysine, phenylalanine, arginine, histidine, caffeine, procaine, pyperidine, morpholine, N-ethylmorpholine or polyamino resins.

"Anion pharmacologically acceptable" salts can be obtained by addition with hydrochloric, hydrobromic, nitric, phosphoric, sulphoric, benzenesulphoric, benzoic,

p-toluenesulphonic, salicylic, citric acids.

Moreover, the present invention relates to pharmaceutical compositions containining compounds of formula (I) or the cation or anion pharmacologically acceptable salts thereof.

Non-limiting examples of the compounds of general formula (I) useful for the pharmaceutical compositions of the present invention are listed in following Table I.

TABLE 1

Compound No.	R	R^1	R^2	R^3
1	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	H	H
2	$(CH_2)_5COOH$	$(CH_2)_6CH_3$	H	H
3	$(CH_2)_7CH_3$	$(CH_2)_6COOH$	H	H
4	$(CH_2)_5COOH$	$(CH_2)_8CH_3$	H	H
5	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	Et	H
6	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2Ph	5-Cl
7	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	2-picolyl	H
8	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2CH_2OH	H
9	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2CH_3NMe	H
10	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2COOH	H
11	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	H	5-Cl
12	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	H	5-MeO
13	$(CH_2)_5COOH$	$(CH_2)_8CH_3$	Et	5-Cl
14	$(CH_2)_5COOH$	$(CH_2)_8CH_3$	CH_2Ph	H
15	$CH=CH(CH_2)_3CH_3$	$(CH_2)_6COOH$	H	H
16	$CH=CHCH(OH)(CH_2)_2CH_3$	$(CH_2)_6COOH$	H	H
17	$CH=CH(CH_2)_3CH_3$	$(CH_2)_6COOH$	Et	H
18	$CH=CH(CH_2)_3CH_3$	$(CH_2)_6COOH$	H	5-Cl
19	$(CH_2)_5COOH$	$CH=CH(CH_2)_5CH_3$	H	H
20	$(CH_2)_5COOH$	$CH=CH(CH_2)_5CH_3$	CH_2COOH	5-MeO
21	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2Ph	H
22	$(CH_2)_5CH_3$	$(CH_2)_6COOH$	CH_2COOEt	H

The pharmacological activity of the products of the invention has been evaluated, for example, by in vitro determining the inhibition of platelet aggregation induced by collagen, arachidonic acid, thrombin on platelet-rich plasma (in the following indicates as PRP) of rat (Table 1) or by ex vivo evaluating in the rat the percent inhibition of platelet aggregation induced by ADP or by collagen (Table 2) according to G.V. Born in Nature 194, 927-929 (1962) and to G.V. Born and Cross in J. Physiol. 168, 178-195 (1963).

The examples and compounds reported below are only exemplificative and are not intended to limit the invention.

1) In vitro determination of the percent inhibition of collagen-induced platelet aggregation on rat PRP.

Tests were carried out on rat PRP (500.000 platelets/mm^3) by addition of a compound of formula (I) or a salt thereof so as to reach a plasma concentration of 10^{-4} M and incubation at room temperature for 9 minutes. After that, collagen 3 mcg/ml was added as the pro-aggregation agent and the percent inhibition of platelet aggregation was measured according to Born and Cross turbidimetric method (Table 2).

2) In vitro determination of the percent inhibition of arachidonic acid-induced platelet aggregation on rat PRP.

The test was carried out as described in item 1), using arachidonic acid 200 µM as the pro-aggregating agent (Table 2).

3) In vitro determination of the percent inhibition of thrombin-induced platelet aggregation on rat PRP.

The test was effected as described in item 1), using thrombin 0.1 U/ml as the pro-aggregating agent (Table 2).

The transmittance measurements were carried out by means of a Chromolog 540 or Elvi 840 aggregometer.

TABLE 2

COMPOUND	% INHIBITION IN RAT OF PLATELET AGGREGATION INDUCED BY:		
	COLLAGEN	ARACHIDONIC ACID	THROMBIN
-sodium 7-(3-hexylindole-2-yl) heptanoate	84.0	57.0	97
sodium 6-(2-heptylindole-3-yl) hexanoate	12	32	100
sodium 7-(3-octylindole-2-yl) heptanoate	21	17	100
sodium 6-(2-nonylindole-3-yl) hexanoate	50	49	100

4) Ex vivo determination of the percent inhibition of ADP-induced platelet aggregation in the rat.

Fasted rats were orally administered with a compound of general formula (I) or a pharmacologically salt thereof in a suitable carrier at a dose of 50 mg/kg. PRP of each animal was added with 2 µM ADP as the pro-aggregating agent and the percent inhibition of platelet aggregation was measured according to Born and Cross turbidimetric method (Table 3).

5) Ex vivo determination of the percent inhibition of collagen-induced platelet aggregation in the rat.

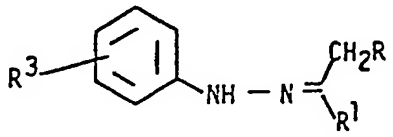
The test was carried out as described in item 4) using 5 mcg/ml collagen as the pro-aggregating agent (Table 3).

TABLE 3

COMPOUND	EX VIVO DETERMINATION IN THE RAT OF THE % INHIBITION OF PLATELET AGGREGATION INDUCED BY:	
	COLLAGEN	ADP
sodium 7-(3-hexylindole-2-yl)heptanoate	77.7	53.9
sodium 7-(3-octylindole-2-yl)heptanoate	29.4	35.5
sodium 6-(2-nonylindole-3-yl)hexanoate	69.6	25.6

The compounds of general formula (I) can be prepared by suitably adapted known methods for the preparation of indoles, for example by the following methods which are also an object of the present invention.

1. Indole compounds of general formula (I) in which R^2=H are prepared by cyclization of the compounds of general formula (II)



(II)

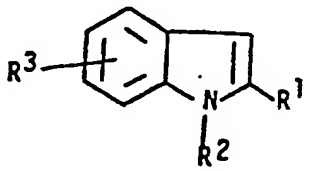
(wherein R, R^1 and R^3 have the above defined meanings) by reaction with inorganic or Lewis acids, such as boron trifluoride, zinc chloride, at high temperatures, possibly in the presence of inert organic solvents.

Compounds of general formula (II) can in their turn be prepared starting from the corresponding ketones (the preparation of which can be carried out by various techniques known to those skilled in the art, e.g. by reacting acid chlorides organocadmium compounds by reaction with the appropriate phenylhydrazine in inert solvents (preferably benzene or toluene) with remotion of the reaction water. It would be still better to prepare <u>in situ</u> such hydrazones, effecting the cyclization reaction in high boiling alcohol solvents using the same ketones as above described and phenylhydrazine hydrochloride.

Nevertheless, the described sequence, which is an

application of the well known Fischer synthesis for indoles, has the drawback that two isomeric compounds form which are often difficult to separe. Moreover, in case of unsaturated derivatives, this procedure not always gives the desired results.

2. Indole compounds of general formula (I) can be prepared by alkylating at the 3-position the compounds of general formula (III)

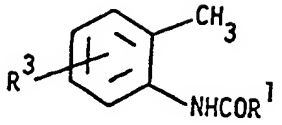


(III)

e.g. when $R^1=(CH_2)_m-X-CHR^4(CH_2)_nR^5$ with m and n = integers from 0 to 8, n+m = an integer from 2 to 10, $X=CH_2$, $R^4=H$, $R^5=COOR^6$, such a reaction can conveniently be carried out with appropriate sodium alkoxides, e.g. hexanoxide using an excess of the corresponding alcohol as the solvent, in autoclave at high temperatures, or when $R^1=(CH_2)_m-X-CHR^4(CH_2)_nR^5$ with m and n = integers from 0 to 8 and n+m = an integer from 4 to 10; $X=CH_2$, $R^4=H$; $R^5=Me$ in high boiling inert solvents (tetralin, p-cymene) using a cyclic lactone such as caprolactone in the presence of bases such as KOH, thereby obtaining a COOH group at the end of the alkyl chain R.

3. Indole compounds of general formula (III) wherein $R^1=(CH_2)_m-X-CHR^4(CH_2)_nR^5$ with m and n = an integer from 0 to 8, m+n = an integer from 2 to 10, $X=CH_2$, $R^4=H$, $R^5=Me$, can be prepared by cyclization of the

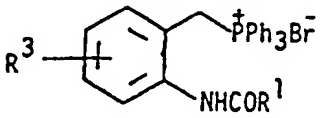
compounds of formula (IV)



(IV)

in the presence of a base such as potassium tert-butoxide at high temperatures, preferably in the absence of a solvent.

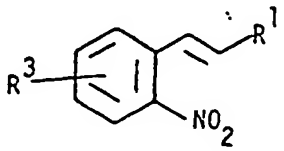
4. Compounds of general formula (III) in which $R^1=(CH_2)_m-X-CHR^4(CH_2)_nR^5$ with m and n = an integer from 0 to 8, m+n = an integer from 2 to 10, $X=CH_2$, $R^4=H$, $R^5=COOR^6$, are prepared by cyclizating the compounds of general formula (V)



(V)

in an organic inert solvent, such as toluene, in the presence of a base, preferably at high temperatures. Said compounds can in their turn be obtained by techniques known to those skilled in the art, e.g. starting from 2-nitro-benzyl bromide or anthranilic alcohol.

5. Compounds of general formula (III) in which $R^1=(CH_2)_m-X-CHR^4(CH_2)_nR^5$ with m and n = an integer from 0 to 8, m+n = an integer from 2 to 10, $X=CH_2$, $R^4=H$, $R^5=Me$ are prepared by cyclizating at high temperatures with $(RO)_3P$ the compounds of general formula (VI)



(VI)

6. Compounds of general formula (I), in which in chains R or R^1 an unsaturation is present, can more easily be obtained starting from indolecarboxyaldehyde by means of a Wittig reaction with $PPh_3^+(CH_2)_nCH_3Br^-$ or $(EtO)_2P(O)CH_2C(O)(CH_2)_nCH_3$.
Particularly, indole-3-carboxyaldehyde derivatives are prepared starting from compounds of general formula (III) by reaction with $POCl_3$ and DMF, extrapolating the procedure described in Org.Synth.Coll. vol.4 pag. 539.

7. Specific R^2 groups can be introduced into compounds of general formula (I) or (III) starting from compounds (I) or (III) themselves in which R^2 is H, by reaction with $Y-R^2$ wherein R^2 is different from H and Y is chlorine, bromine, iodine or mesyl in a suitable solvent (DMF, DMSO, HMPT, THF, anhydrous alcohols) in the presence of appropriate organic or inorganic bases such as potassium tertbutylate, sodium methylate, sodium ethylate, sodium hydride, sodium amide, potassium hydroxide, preferably sodium hydride.

8. Compounds of general formula (I) in which R^6=H, R^7=COOH can be transformed into the pharmacologically acceptable addition salts thereof by reaction, for example, with compounds of general formula R^9OM in which M is an alkali metal and R^9 is H or a C_1-C_6 alkyl group, preferably methyl or ethyl, in a suitable solvent, followed, if necessary, by evaporation of part or all the solvent and filtration of the solid product, optionally after precipitation with an

appropriate solvent selected from acetonitrile, ether, hexane, in which the salt is unsoluble.

The following examples and compounds further illustrate the present invention and are not intended to limit the spirit and scope thereof.

EXAMPLE 1

Preparation of methyl 7-(3-hexylindole-2-yl)heptanoate

34.2 g (0.32 mole) of phenylhydrazine were added to a solution of methyl 8-ketopentadecanoate (85.3 g, 0.32 mole) in toluene (170 ml) and the reaction mixture was refluxed for 3.5 hours with a Dean-Stark apparatus, to remove water formed during the reaction. After that the mixture was dried and evaporated to dryness and the product was placed into a flask, added with 405 g of anhydrous $ZnCl_2$ and heated to 180°C in a pre-heated bath, stirring at this temperature for about 10 minutes from the development of the first white smokes, 350 g of silica were added and the mass was vigorously stirred, then it was cooled, silica was washed more times with ethyl acetate, the organic solution was washed more times with water, dried and evaporated to dryness. 71 g of a product consisting of the mixture of the two isomers were obtained. 24.4 g of the title product, in form of a viscous oil, were obtained by column chromatography (silica gel, eluted with hexane/ethyl acetate 92/8).

Rf (TLC on silica gel, eluent hexane/ethyl acetate 8:2)=0.4

IR (film) 3400, 2920, 1745, 1465 cm^{-1}

NMR ($CDCl_3$) δ 0,9 (3H, t); 1,4 (16H, broad s); 2,3 (2H, t); 2,7 (4H, m); 3,75 (3H, s); 7,0-7,6 (4H, aromatic);

7,7 (1H, NH).

EXAMPLE 2

Preparation of methyl 7-(3-hexylindole-2-yl)heptanoate

60.5 g of phenylhydrazine hydrochloride were added to a solution of methyl 8-ketopentadecanoate (113.6 g, 0.42 mole) in tert-butanol (2 l) and the mixture was refluxed under nitrogen atmosphere for 18 hours. After that the reaction mixture was cooled, solvent was evaporated off under vacuum, the residue was taken up into CH_2Cl_2, the unsoluble solid was filtered off, the solution was washed with water to neutral and, after drying, evaporated to dryness. The residue (143.1 g) consisted in the mixture of the two isomers, which were separated by column cromatography (silica gel eluted with hexane/ethyl acetate 92/8) to obtain 66 g of the title product, whose spectral characteristics are the same as those of the product of Example 1.

EXAMPLE 3

Preparation of sodium 7-(3-hexylindole-2-yl)heptanoate

10 g of the product prepared as described in Example 2 were dissolved in a mixture of THF (950 ml) and 0,1 N NaOH (640 ml) and refluxed for 18 hours. Then the mixture was cooled, THF was removed under vacuum, the remaining aqueous solution was acidified to pH = 4 and extracted with ethyl ether, dried and evaporated to dryness under vacuum, to obtain 8 g of 7-(3-hexylindole-2-yl)heptanoic acid having a 98% titre. Said acid was dissolved in MeOH (60 ml) and added with 4.9 ml of MeONa in 5N MeOH. 30 Minutes after the clear solution was concentrated and treated with hexane to yield 7.3 of a

white solid.

IR (KBr) 3400, 2900, 1610 cm^{-1}

NMR (D_2O) δ 0,8 (3H, t); 1,3 (16H, broad s); 2,2 (2H, t); 2,6 (4H, t); 6,9-7,4 (4H, aromatic).

EXAMPLE 4

Preparation of methyl 6-(2-heptylindole-3-yl)hexanoate

Following the same procedure as in Example 2, but recovering the other isomeric product from the separation carried out by column chromatography, 63 g of the title compound were obtained in form of a viscous oil, whose spectral analysis was analogous to that of the isomer of Example 2, except for Rf (TLC on silica gel, hexane/ethyl acetate 8:2)=0.6.

EXAMPLE 5

Preparation of sodium 6-(2-heptylindole-3-yl)hexanoate

Following the same procedure of Example 3, but starting from the product obtained in Example 4, 7 g of the title compound were prepared.

IR 3400, 2920, 1620, 1460 cm^{-1}

NMR (D_2O) δ 0,85 (3H, t); 1,2 (16H, m); 2,2 (2H, t); 2,6 (4H, m); 6,8-7,5 (4H, m).

EXAMPLE 6

Preparation of methyl 7-(5-chloro-3-hexylindole-2-yl)heptanoate

Following the same procedure of Example 2, starting from methyl 8-ketopentadecanoate, but using 4-chlorophenylhydrazine hydrochloride instead of phenylhydrazine, after separation of the mixture of the two isomers, 43.8 g of the title compound were obtained in form of an oil.

IR 3400, 2920, 1745, 1460 cm^{-1}

NMR ($CDCl_3$) δ 0,9 (3H, t); 1,4 (16H, m); 2,3 (2H, t); 2,8 (4H, m); 3,75 (3H, s); 6,9-7,6 (3H, m); 7,8 (1H, NH).

EXAMPLE 7

Praparation of 2-hexylindole

30 g of 1-(2-nitrophenyl)-octene-1 (prepared by a Wittig reaction of 2-nitrobenzaldehyde with heptyltriphenylphosphonium bromide) and 150 ml of triethyl phosphite were refluxed (160°C) for 18 hours, then the triethyl phosphite excess was distilled under high vacuum as well as triethylphosphate formed during the reaction, the kettle residue was taken up into water and extracted with diethyl ether. The ether solution was evaporated to dryness and the crude product was purified by chromatography, to yield 9 g of the title compound (36% yield).

NMR ($CDCl_3$) δ 0,85 (3H, t); 1,3 (8H, m); 2,5 (2H, t); 6,1 (1H, s); 6,9-7,5 (4H, m).

EXAMPLE 8

Preparation of 2-nonylindole

A mixture of decanoyl-o-toluidine(2 g 7,7 mmole)and potassium tert-butylate in a flask under slight nitrogen stream was placed into a sand bath heated to 240°C and temperature was quickly raised to 300°C. This temperature was maintained for 15 minutes, then the mixture was cooled, taken up into water, acidified with 3N HCl and extracted with ether. The ether solution was dried and evaporated to dryness. From the solid residue, by crystallization, 1.1 g (59% yield) of the title compound was obtained.

NMR ($CDCl_3$) δ 0,85 (3H, t); 1,3 (14H, s); 2,5 (2H, t); 6,1 (1H, s); 6,9-7,5 (4H, m).

M.p. = 58-60°C

EXAMPLE 9

Preparation of methyl 7-(indole-2-yl)-heptanoate

a) preparation of 2-(methoxycarbonylhexylcarbonylamino)--benzyl triphenylphosphonium bromide

A solution of o-aminobenzyl triphenylphosphonium bromide (38 g, 0.08 mole) in CH_2Cl_2 (65 ml) and pyridine (15.2 ml) cooled at 0-5°C, was added dropwise with suberic acid monochloride monoester (18 g, 0.08 mole) dissolved in CH_2Cl_2 (15 ml) and said solution was stirred for 18 hours at room temperature, thereafter it was diluted with more methylene chloride and washed with HCl, then with brine, till neutrality. Then the reaction mixture was dried and evaporated to dryness; m.p. 84-86°C.

b) preparation of methyl 7-(indole-2-yl)heptanoate

20 g of the product prepared in a) were dissolved in toluene (90 ml) at 80°C and 4.2 g of potassium tert-butylate were added portionwise during about 5 min. After that the reaction mixture was heated to reflux for some minutes, then cooled, the unsoluble solid was filtered, washed with ether and the organic phases were combined and evaporated to dryness.

By column chromatography, 9 g of the starting compound and 3.8 g of the title compound (46% yield) were obtained.

IR (nujol) 3400, 1745 cm^{-1}

NMR ($CDCl_3$) δ 1,45 (8H, m); 2,3 (2H, t); 2,7 (2H, t); 3,7 (3H, s); 6,3 (1H, s); 7,1-7,6 (4H, m); 7,9 (1H, NH).

EXAMPLE 10

Preparation of 7-(3-hexylindole-2-yl)heptanoic acid

4 g of the product prepared as described in Example 9 were dissolved in n-hexanol (80 ml) in an autoclave and added with 2.6 g of sodium metal in small pieces. The mixture was slightly heated till complete dissolution of sodium then the autoclave was closed and heated to 215°C for 15 hours. The mixture was cooled, diluted with ether, washed with 1N HCl, then with water to neutrality, dried and evaporated to dryness under vacuum. The hexanol excess was distilled off to obtain 3.1 g (57%) of the title compound.

Elemental analysis: $(C_{21}H_{32}O_2N)$

calculated: C=76.36; H=9.70;N=4.24

found : C=76.45; H=9.78; N=4.15

EXAMPLE 11

Preparation of 7-(3-octylindole-2-yl)heptanoic acid

Following the same procedure as described in Example 11, but using n-octanol, the title compound was obtained.

IR (film) 2930, 1710, 1465 cm^{-1}

NMR ($CDCl_3$) δ 0,9 (3H, t); 1,4 (20H, broad s); 2,5 (6H, m); 7,0-7,7 (4H, m); 10,2 (1H, s).

EXAMPLE 12

Preparation of 6-(2-nonylindole-3-yl)hexanoic acid

2 g of nonylindole (prepared as described in Example 8), 1.1 g of caprolactone, 0.8 g of KOH (85%) and 10 ml of p-cymene were placed into an autoclave which was heated to 240°C for 15 hours. The reaction mixture was cooled, diluted with water, acidified and extracted with ether. Following the usual work-up, 1.1 g of the title compound was obtained.

IR 3400, 2940, 1710, 1465 cm^{-1}

NMR ($CDCl_3$) δ 0,8 (3H, t); 1,25 (20H, s); 2,5 (6H, m); 7,0-7,7 (4H, m); 10,0 (1H, s).

EXAMPLE 13

Preparation of 7-(3-hexyl-N-ethylindole-2-yl)heptanoic acid

To a suspension of NaH (60%, 0.530 g) in THF (5 ml) a solution of methyl 7-(3-hexylindole-2-yl)heptanoate (2.3 g) in THF (5 ml) was added and the mixture was refluxed for 15 min., then cooled and added dropwise with an ethyl bromide solution (0.73 g) in THF (5 ml). The solution was refluxed for 3 hours, then cooled, added with water and extracted with ether. The extracts were washed till neutrality, dried and evaporated to dryness.

By chromatography on a silica gel column eluting with hexane/ethyl acetate 6:2, 1.2 g of the title compound was obtained.

NMR ($CDCl_3$) δ 0,8 (3H, s); 1,4 (19H, s+t); 2,4 (2H, t); 2,7 (4H, m); 4,1 (2H, q); 7,0-7,7 (4H, m); 10,6 (1H, s).

EXAMPLE 14

Preparation of methyl 7-(N-benzyl-5-chloro-3-hexylindole--2-yl)-heptanoate

The indole derivative prepared as described in Example 6 (3 g, 8.7 mmoli) in DMSO (2 ml) was added to a KOH solution (86%, 2.3 g) in DMSO (17 ml). The reaction mixture was stirred for 45 min., then cooled in an ice-bath and added with benzyl bromide (3 g, 17.4 mmoli). The solution was stirred for 45 min. at room temperature, poured into water, acidified with 1N HCl and extracted with methylene chloride. From the organic phase a crude

product was obtained which was purified by chromatography, obtaining 1.8 g of the title compound as an oil.

NMR ($CDCl_3$) δ 0,8 (3H, t); 1,25 (16H, m); 2,2 (2H, t); 2,6 (4H, m); 3,6 (3H, s); 5,2 (2H, s); 6,8-7,7 (8H, m).

EXAMPLE 15

Preparation of methyl 7-(3-hexyl-N-(ethoxycarbonylmethyl)indole-2-yl)heptanoate

Following the same procedure described in Example 14, starting from the product obtained as described in Example 2, by reaction with ethyl bromoacetate, the product title was obtained in form of an oil.

IR (film) 3400, 2920, 1745, 1460 cm^{-1}

NMR ($CDCl_3$) δ 0,9 (3H, t); 1,2 (19H, m); 2,4 (2H, t); 2,7 (4H, m); 3,7 (3H, s); 4,1 (2H, q); 4,5 (2H, s); 7-7,5 (4H, m).

EXAMPLE 16

Preparation of sodium 7-(3-hexenylindole-2-yl)heptanoate

a) preparation of methyl 7-(3-formylindole-2-yl)heptanoate.

Methyl 7-(indole - 2-yl)heptanoate prepared as described in Example 9 (10 g, 0.038 mole) dissolved in DMF (25 ml) was added during about 1 hour to a solution of phosphorus oxychloride (4 ml) in DMF (13 ml) cooled to 0-5°C. The reaction mixture was heated to 35°C under stirring for 1 hour, to obtain a viscous solution which was added with 13 g of triturated ice and subsequently with 5 ml of water and 17 g of NaOH in 50 ml of water. The suspension was quickly heated to the boiling point, then cooled and left to stand overnight.

The reaction mixture was then diluted with water and extracted with ether, which was evaporated off under vacuum to yield 10 g of 7-(3-formylindole-2-yl)heptanoic acid which, for the subsequent reaction, must be esterified, e.g. with diazomethane.

IR (film) 3400, 2920, 1750, 1465 cm^{-1}

NMR (DMSO) δ 1,35 (6H, broad s); 2,3 (2H t); 3,0(2H, t); 3,6 (3H, s); 7,0-7,5(4H, m); 8,0 (1H, m), 10,0 (1H, s).

M.p. = 199-121°C

b) protection

4-dimethylaminopyridine (0.4 g) and ditert-butyldicarbonate (9 g) were added to 10 g of methyl 7-(3-formylindole-2-yl)heptanoate prepared in point a) dissolved in CH_3CN (80 ml) and the mixture was stirred at 20°C for 1 hours. Then 1.2 g of diethylaminoethylamine was added to the mixture, which was stirred for 10 min., diluted with 1M $KHSO_4$ and extracted with ethyl ether twice. The organic phase was washed with $KHSO_4$, then with $NaHCO_3$, finally with water, dried and evaporated to dryness. 16 g of methyl 7-(1-tert-butoxy-carbonyl-3-formylindole-2-yl)heptanoate were obtained, in form of a colorless liquid.

NMR ($CDCl_3$) δ 1,4 (8H, m); 1,7 (9H, s); 2,3 (2H, t); 3,3 (2H, t); 3,7 (3H, s); 7,0-8,2 (4H, m); 10,2 (1H, s).

c) condensation

4.0 ml of 2.5N butyl lithium in hexane were added to 4.1 g of pentyl triphenylphosphonium bromide in 25 ml of anhydrous THF and cooled to 0-5°C stirring for some minutes. Then 3.36 g of the product obtained as described in point b) dissolved in THF (50 ml) were added at the

same temperature continuing stirring for 3 hours. After that, water was added to the mixture which was extracted with ether. The organic phase was dried and evaporated to dryness under vacuum, to yield 3.4 g of a crude product which was purified by column chromatography (silica gel eluted with hexane/ethyl acetate 8:2) to obtain 2.1 g of a product.

d) hydrolysis

The obtained product was dissolved in THF and added with 3 equivalents of sodium methoxide (in methanol) and stirred at room temperature for 45 min. Then the mixture was diluted with water and extracted with ethyl ether. The organic solution was dried and evaporated to dryness to obtain the methyl ester corresponding to the title compound, which was dissolved in methanol and treated with an aqueous solution of potassium carbonate. The reaction mixture was stirred for 2 hours, then cooled, methanol was evaporated under reduced pressure, then the mixture was acidified with 2N HCl to pH = 3 and extracted with ethyl ether. The organic solution was dried and evaporated to dryness to obtain the acid corresponding to the title compound. Following the same procedure as described in Example 3 the desired sodium salt was obtained.

NMR (D_2O) δ 0,9 (3H, t); 1,3 (12H, m), 2,4 (6H, m); 6,1 (2H, m); 7-7,4 (4H, m).

EXAMPLE 17

Preparation of sodium 7-(3-(3-hydroxy)hexenylindole-2--yl)heptanoate

5 g of 2-oxopentyl dimethylphosphonate dissolved in

10 ml of DMF were added dropwise to a suspension of NaH (80%, 0.78 g) in dimethoxyethane (DME) (150 ml) cooled to -10°C. After 20 minutes under strong stirring, 7.17 g of the aldehyde prepared as described in Example 16 b) were added at the same temperature. After that temperature was left to raise to the room value and the mixture was refluxed for 1 hour, then cooled, diluted with 1N NaOH and extracted with CH_2Cl_2 (3x100 ml). The organic phases were evaporated to dryness, to give a product which was purified by column chromatography (silica gel, hexane/ethyl acetate 7:3) then dissolved in a mixture of methanol THF 1:1 (400 ml). To said solution 2 g of $NaBH_4$ were added portionwise in 1 hour. After that acetone was added, the mixture was concentrated to small volume, taken up into CH_2Cl_2, washed with a NH_4Cl saturated solution, then with water, dried and evaporated to dryness. Following a procedure similar to that of Example 16, point d), 2.1 g of the title compound were obtained. NMR (D_2O) δ 0,9 (3H, t); 1,25 (12H, m); 2,3 (4H, m); 5,4 (1H, m); 6,25 (2H, m); 7-7,5 (4H, m).

EXAMPLE 18

2.98 g (8.7 mmole) of methyl 7-(3-hexylindole-2-yl)-heptanoate, prepared as described in Example 2, in DMSO (2 ml) were added to a solution of KOH (86% 2.3 g) in DMSO (17 ml) stirring for 45 min. Then the mixture was cooled with an ice bath and added with 2-bromoethyltetrahydropyranyl ether (3.64 g, 17.4 mmole) during 15 min. The mixture was stirred at room temperature for 2 hours, poured into water and extracted with ethyl ether. The organic phase was dried, evaporated to dryness and

dissolved in ethanol (100 ml) and treated with pyridine p-toluenesulfonate (4.68 g) at 55°C for 3 hours. Solvent was evaporated off. The residue was purified by chromatography to obtain 2.7 g of the ethyl ester corresponding to the title compound. By basic hydrolysis, as described in Example 3, 2.1 g of the title compound were obtained (65% yield).

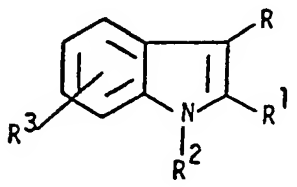
NMR ($CDCl_3$) δ 0,9 (3H, t); 1,45 (16H, m); 2,3 (2H, t); 2,7 (4H, m); 3,8 (2H, t); 4,1 (2H, t); 7,0-7,7 (4H, m).

The compounds of the present invention are preferably administered in form of pharmaceutical compositions in mixture with one or more pharmacologically acceptable diluents, excipients, binders, preservants, stabilizers, flavoring agents.

Preferably, they are administerd by the oral route (e.g. in form of tablets, capsules, granules, syrups, etc.) or by the parenteral route (intravenous or intramuscular). The dosage will depend on the symptoms, sex, body weight and conditions of the patient as well as on the frequency and the administration route, but generally the compound of the invention will be administered orally to an adult at a 1 to 2.000 mg daily dosage, preferably 10 to 1.000 mg, in a single dose or in doses subdivided during 24 hours.

CLAIMS

1. Indole derivative of general formula (I)



(I)

as well as the possible optical and/or geometric isomers, wherein R and R^1, which can be the same or different, are: $(CH_2)_m$-X-$CHR^4(CH_2)_nR^5$, in which m and n are an integer 0 to 8 and m + n are an integer 2 to 10; X=CH_2, CH=CH; R^4=H,OH; R^5=Me, CH_2OH, CHO, tetrazol, CH_2NH_2, $COOR^6$; R^6=H,Me,Et, benzyl, pivalyl groups or other groups forming a pharmacologically acceptable ester;
R^2 is H; a straight or branched chain (C_1-C_6) alkyl; benzyl, 2-picolyl, 3-picolyl, 4-picolyl groups; $(CH_2)_pR^7$ with p comprised from 1 to 6, in which R^7=COOH, NHR^8, OH, SR^8 and R^8 in its turn is a straight or branched chain (C_1-C_6) alkyl;
R^3 is H, halogen, straight or branched (C_1-C_6) alkoxy; and the pharmacologically acceptable salts thereof.

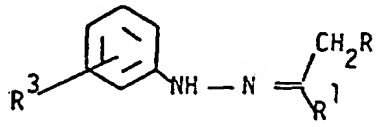
2. Indole derivative as claimed in claim 1, wherein R is an alkyl or alkenyl chain containing at least 4 carbon atoms.

3. Indole derivative as claimed in claim 1 or 2, wherein R^1 is an alkyl or alkenyl chain containing at least 4 carbon atoms.

4. Indole derivative as claimed in any preceding claim wherein R^5 is a $COOR^6$ group.

5. Indole derivative as claimed in claim 3 wherein R^5 is a $COOR^6$ group.

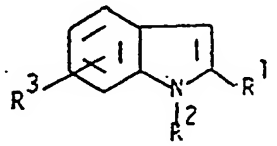
6. A process for the preparation of an indole derivative of formula (I) as claimed in any one of claims 1 to 5, wherein R^2=H, by cyclization of a compound of general formula (II)



(II)

with inorganic acid and/or Lewis acid, preferably at a high temperature.

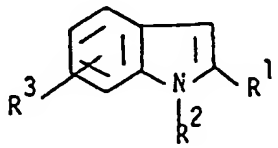
7. A process for the preparation of an indole derivative of formula (I) as claimed in any one of claims 1 to 5, by alkylation of a compound of general formula (III)



(III)

with a sodium alkoxide, preferably at a high temperature and in the presence of the corresponding alcohol itself as solvent, wherein R^1, R^2 and R^3 are as defined in claim 1.

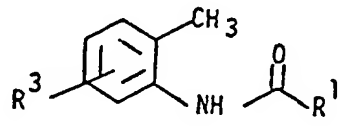
8. A process for the preparation of an indole derivative of formula (I) as claimed in any one of claims 1 to 5, by alkylation of a compound of general formula (III)



(III)

with a cyclic lactone in the presence of base and inert solvent, preferably at a high temperature.

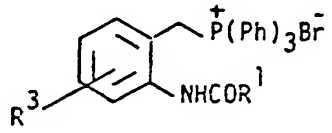
9. A process for the preparation of an indole derivative of formula (III) as defined in claim 7, useful for the preparation of an indole derivative of formula (I) as claimed in any one of claims 1 to 5, by cyclization of a compound of general formula (IV)



(IV)

in the presence of base with or without solvent, preferably at a high temperature.

10. A process for the preparation of an indole derivative of formula (III) as defined in claim 7, useful for the preparation of an indole derivative of formula (I) as claimed in any one of claims 1 to 5, by cyclization of a compound of general formula (V)

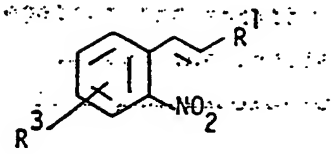


(V)

in the presence of base, in inert organic solvent, preferably at a high temperature.

11. A process for the preparation of an indole derivative of formula (III) as defined in claim 7, useful for the preparation of an indole derivative of formula (I), as claimed in any one of claims 1 to 5,

by cyclization of a compound of general formula (VI)



(VI)

with triethyl phosphite as the reactant and as the solvent, preferably at a high temperature.

12. A process for the preparation of a compound of general formula (I) wherein X=CH=CH, as claimed in any one of claims 1 to 5, starting from a compound of general formula (III) as defined in claim 7, by reaction with $POCl_3$ and DMF, protection of indole-3-carboxyaldehyde at the 1-position with acetyl chloride, Wittig condensation with $PPh_3^{\oplus}(CH_2)_nCH_3Br^{\ominus}$ or $(EtO)_2P(O)CH_2C(O)(CH_2)_nCH_3$, and hydrolysis of the acetyl group with potassium hydroxide.

13. A process for the preparation of a compound of general formula (I) or (III) as previously defined, wherein R^2 is a C_1-C_6 straight or branched alkyl chain; benzyl, 2-picolyl, 3-picolyl, 4-picolyl; $(CH_2)_pR^7$ where p is from 1 to 6, in which R^7=COOH, NHR^8, OH, SR^8 and R^8 is a C_1-C_6 straight or branched alkyl chain, starting from a compound of general formula (II) or (III) as previously defined, wherein R^2=H, by reaction with a compound of formula Y-R^2 in which R^2 is other than hydrogen and Y is chlorine, bromine, iodine, or mesyl, in the presence of organic and/or inorganic base and appropriate solvent comprising one or more of: DMF, DMSO, HMPT, THF, and anhydrous alcohols.

14. A process as claimed in any one of claims 6 to 13, substantially as herein described and/or exemplified in any example.

15. An indole derivative as claimed in any one of claims 1 to 5 or a pharmacologically acceptable salt thereof having anti-platelet aggregation and/or other antithrombotic properties, wherein the R, R^1, R^2 and R^3 groups are defined as follows:

$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=H$, $R^3=H$;
$R=(CH_2)_5COOH$, $R^1=(CH_2)_6CH_3$, $R^2=H$, $R^3=H$;
$R=(CH_2)_7CH_3$, $R^1=(CH_2)_6COOH$, $R^2=H$, $R^3=H$;
$R=(CH_2)_5COOH$, $R^1=(CH_2)_8CH_3$, $R^2=H$, $R^3=H$;
$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=Et$, $R^3=H$;
$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=CH_2Ph$, $R^3=5\text{-}Cl$;
$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=CH_2COOH$, $R^3=H$;
$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=H$, $R^3=5\text{-}Cl$;

$R = CH=CH(CH_2)_3CH_3$, $R^1=(CH_2)_6COOH$, $R^2=H$, $R^3=H$;
$R = CH=CHCH(OH)(CH_2)_2CH_3$, $R^1=(CH_2)_6COOH$, $R^2=H$, $R^3=H$;
$R=(CH_2)_5CH_3$, $R^1=(CH_2)_6COOH$, $R^2=CH_2CH_2OH$, $R^3=H$.

16. An indole derivative substantially as herein before described and/or as exemplified in any example.

17. Pharmaceutical composition having anti-platelet aggregation and antithrombotic activities, characterized in that they contain as the active ingredient an indole derivative of general formula (I) as claimed in claim 1 or a pharmacologically acceptable salt thereof.

18. Pharmaceutical compositions having anti-platelet aggregation and antithrombotic activities, containing as the active ingredient indole derivative as claimed in claim 15 or 16 or a pharmacologically acceptable salt thereof.

19. A pharmaceutical composition comprising an indole derivative as claimed in any one of claims 1 to 5 or 14 or 15 substantially as herein described and exemplified in any example.

20. Use of an indole derivative as claimed in any one of claims 1 to 5 or 14 or 15 in medicine.

21. Use of an indole derivative as claimed in any one of claims 1 to 5 or 14 or 15, or a composition as claimed in any one of claims 16 to 19, in the manufacture of a medicament for use in combating the formation of thrombi.

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